CHAPTER 15 **EUROCHAM HEALTHCARE FORUM**

OVERVIEW

Vietnam continues to attract great interest from leading international companies in the life sciences sector. The EuroCham Healthcare Forum – with members from the innovative pharmaceutical industry (Pharma Group), the International Quality Medicines – Generic and Biosimilar industry (IQMED – Generic and Biosimilar SC), and the Medical Devices and Diagnostics industry (MDD SC) – applauds the continued efforts of the Government to improve the healthcare sector in Vietnam.

The EuroCham Healthcare Forum sees an opportunity to further strengthen dialogue and partnership with the Government, developing an attractive investment environment and a top-tier healthcare system for Vietnamese patients.

I. WORKING TOGETHER TOWARDS LIFE SCIENCES SECTOR DEVELOPMENT

Relevant authorities: Office of Government (OOG), Ministry of Health (MOH), Ministry of Industry and Trade (MOIT), Ministry of Planning and Investment (MPI)

Issue description

The Vietnamese Government has made impressive progress over the last two decades in improving health for citizens. As the Government's healthcare goals expand to address not only the people's basic and complex needs for quality services and products, but also to strengthen the economic value generated by the sector, there is an opportunity for Vietnam to transform the whole sector and become a leading country in ASEAN for high-quality healthcare in the next 15 years.

Through dialogue with the Vietnamese Government, the international healthcare industry is encouraged by (a) Vietnam's openness for foreign investment and fair access to the Vietnamese market (b) the acknowledgement of our critical role in bringing high-quality products for prevention, diagnosis, treatment and monitoring, and (c) the emerging incentives to transfer global knowledge and capabilities to local and domestic enterprises in Vietnam. The EuroCham Healthcare Forum believes that the ratification of the EU-Vietnam Free Trade Agreement, which is a major achievement, will also further benefit patients and foster trade.

Potential gains/concerns for Vietnam

Vietnam has the opportunity to build a high-value, self-sustaining life sciences sector and position itself as an attractive investment destination in ASEAN. The EuroCham Healthcare Forum stands ready to have a solution-oriented dialogue with the Government on the above enablers, with the overarching objective to develop an attractive investment environment and a sustainable healthcare system.

Recommendations

The following are needed to make such a strategy a reality:

- Strengthen the dialogue between Government, industry and relevant stakeholders to identify holistic policies that, on the one hand, address short-term issues that arise and, on the other hand, ensure benefits for patients, Government and industry alike, while simultaneously and jointly implementing recent international trade agreements successfully;
- Create a predictable, sustainable and outward-looking legal framework for foreign companies to operate and become long-term partners in Vietnam. This should include incentives that encourage long-term investment from MNCs for local manufacturing, technology transfer, investments in local capabilities and medical education; and

- Establish an inter-Ministerial Taskforce under the leadership of an appointed senior Government representative to develop a holistic approach for sector development. Bringing together key actors including regulators, industry, academia, and economic experts to work with the Government toward this goal will stimulate new investment in the short- to medium-term, and upgrade the quality standards and capability of Vietnam's healthcare in the long-term.

II. CONTINUE STRENGTHENING ETHICAL STANDARDS AND COMPLIANCE IN HEALTHCARE TO ENHANCE TRUST AND INTEGRITY

Relevant authorities: Ministry of Health (MOH), Vietnam Medical Association (VAM), Vietnam Women Union (VWU), Vietnamese Pharmaceutical Association (VPA), Vietnam Pharmaceutical Companies Association (VPCA), Vietnam Medical Equipment Association (VMEA)

Issue description

The Vietnamese healthcare landscape is evolving rapidly. Together, trust and integrity in Vietnam play an increasingly important role in shaping relationships between healthcare professionals and the pharmaceutical and medical devices industry that truly serves the best interest of patients. EuroCham Healthcare Forum members believe that, with our global experience and our strong ethical values and practices, we can bring meaningful contributions in promoting high ethical standards, fairness, integrity and transparency amongst all actors in healthcare.

Through our industries' self-regulated Codes of Ethics, Pharma Group, IQMED – Generic and Biosimilar SC, and MDD SC have established and upheld international ethical standards as the basis for our members' activities in Vietnam. We continue to proactively monitor global standards, and have updated our respective Codes in the recent months, to set the bar even higher. These Codes (i) make patients our first priority, and (ii) promote scientific and educational activities with the highest ethical global standards. Particularly for 2019, Sector Committees under EuroCham Healthcare Forum have obtained significant achievements in the development of our industries' self-regulated Codes of Ethics. The new Codes of Pharma Group and IQMED - Generic and Biosimilar took effect in Quarter 1 of 2019, while MDD SC had its first Code coming into force on the 2nd of October 2019.

Potential gains/concerns for Vietnam

We trust that commitments to high ethical standards among all actors in healthcare benefit not only Vietnamese patients, but also promote responsible and fair competition, leading to a more attractive investment environment in Vietnam.

Recommendations

We thank the Ministry of Health and the Government for their attention, and seek support to our efforts in promoting high ethical and compliance standards, towards the development of a higher-quality healthcare system in Vietnam, through:

- Industry associations – foreign and local – to adopt industry self-regulated Codes of Ethics with the same high ethical standards. Pharma Group, IQMED – Generic and Biosimilar SC and MDD SC look forward to sharing our best practices and the latest Codes of Ethics with other partners in healthcare; and

- Enhance dialogues with all stakeholders in healthcare, including the medical community, to promote high ethical standards. In September 2017 in Hanoi, we proudly signed the Consensus Framework for Ethical Collaboration in Vietnam with the Vietnam Medical Association, Vietnam Women Union, Vietnamese Pharmaceutical Association, Vietnam Pharmaceutical Companies Association, Vietnam Medical Equipment Association and Healthcare Committee under American Chamber of Commerce in Vietnam. EuroCham Healthcare Forum believes the Consensus Framework, which encourages signatories to develop self-regulated codes and principles of ethical collaboration and interactions and at the same time targeting a favourable environment for all relevant stakeholders to enhance dialogue, will be the perfect platform for this joint effort.

III. ENABLING PUBLIC-PRIVATE PARTNERSHIP TO DELIVER HIGH-QUALITY HEALTHCARE SERVICES AND A SUSTAINABLE HEALTHCARE SYSTEM FOR VIETNAM

Relevant authorities: Ministry of Health (MOH), Ministry of Planning and Investment (MPI), Ministry of Justice (MOJ)

Description

With a fast-ageing population, the healthcare sector in Vietnam is at an inflection point: as incomes rise, access to Universal Healthcare Coverage (UHC) continues to expand, infrastructure investments by the Government are increasing, and demand for quality health products and services will continue to rise. This creates an increasing need for a more active private sector and for Public-Private Partnerships (PPPs) to develop healthcare services that enhance capabilities and capacity of delivering effective disease management.

Potential gains/concerns for Vietnam

Service-based Public-Private Partnerships (PPPs) can unlock further contribution from the private sector towards an inclusive, forward-looking and sustainable healthcare system for the benefit of Vietnamese people.-

Homecare is an emerging topic to which more attention should be given. The number of patients needing treatment and the overcrowding of hospitals are challenges that MOH aims to overcome. With the limited bed capacity of Vietnamese hospitals, there is an imbalance of 'supply and demand'. Even healthcare systems with greater bed capacity have established homecare services to improve the follow-up of chronic and long-lasting diseases for patients who return to their homes to continue treatment after being discharged from hospital. Patients in Vietnam are currently overburdened with high out-of-pocket payments and, therefore, require affordable treatment options. However, affordable treatment should not be at the cost of quality.

Recommendations

Service-based Public-Private Partnerships (PPPs)

Enable a legal framework (guiding Circular of MOH) for innovative (service-based) PPPs in healthcare and integration into the National Healthcare Financing Strategy. Three main areas of focus are recommended:

- Capability building and development of human resources (including nursing staff, pharmacists and labs physicians) and healthcare facilities management (specifically at the grassroots and provincial level);
- Capacity building (including diagnostics, monitoring, patient records, community health stations, dialysis, etc.); and
- Enhancement of the role of disease prevention (i.e.: early monitoring, disease management for communicable and non-communicable diseases; multidisciplinary teams).

As a pilot phase, and in order to identify potential shortlisted feasible projects as well as to lay the foundation for this partnership, EuroCham Healthcare Forum suggests signing a Memorandum of Understanding with MOH.

Homecare

We believe that Vietnam should support the creation and development of a professional homecare scheme that empowers patients' access to treatment with the involvement of healthcare professionals, in order to reduce the number of hospital visits, especially by patients with chronic diseases. Homecare can empower patient access to treatment, can help to address the problem of overcrowded hospitals, optimise public spending on chronic diseases and mitigate out-of-pocket healthcare spending for households. At the same time, it can help to improve quality of life for all patients suffering from chronic diseases. We are willing to support the development of a homecare scheme together with the Government.

ACKNOWLEDGEMENTS

EuroCham Healthcare Forum

CHAPTER 15A **INTERNATIONAL QUALITY MEDICINES – GENERIC AND BIOSIMILAR**

PART 1: GENERIC

OVERVIEW

The International Quality Medicines – Generic and Biosimilar is a pharmaceutical Sector Committee established under the EuroCham Healthcare Forum[1] in August 2016. The IQMED - Generic and Biosimilar Sector Committee includes FDI or foreign pharmaceutical companies with head offices based in ICH[2] countries and representative offices in Vietnam. Some members company are also manufacturing locally directly or with local partners. Our companies all have products marketed in a minimum of 10 countries in Asia Pacific (APAC), the EU and North America and have 50 per cent of their portfolio revenue categorised in Originator, Generic Group 1 and Generic Group 2 as current tender regulation or with Bio-Equivalence/Bio-Availability (BE/BA) from the EU.

All the IQMED - Generic and Biosimilar members are strongly committed to the common mission of delivering affordable, high-quality, sustainable and trusted off-patent medicines and services to Vietnamese people. Millions of Vietnamese patients are using our members' products every day.

Key activities of the IQMED - Generic and Biosimilar Sector Committee focus on policy advocacy and collaboration with key healthcare stakeholders such as the Government, providers and payers in Vietnam in order to build efficient legal frameworks and implementation platforms.

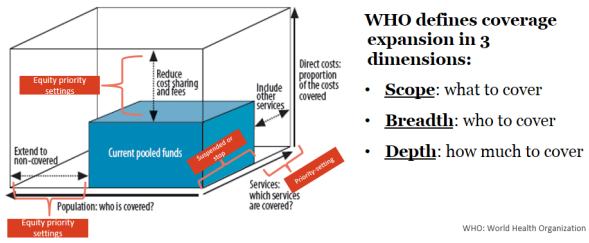
AFFORDABLE TREATMENT OPTIONS FOR VIETNAMESE PATIENTS

Relevant authorities: Ministry of Health (MOH), Vietnam Social Security (VSS), National Assembly (NA) – Committee on Social Affairs.

Issue description

One of the key healthcare objectives of the Vietnamese Government is universal coverage. According to Vietnam Social Security (VSS), by the end of August 2019, 89.6 per cent of the Vietnamese population has been enrolled and given access to the healthcare reimbursement system.[3] The expansion of coverage has not only enrolled more patients but also provided better benefits and reduced patients' self-pay.

Figure 5: Universal Healthcare Coverage 3-Dimensional Expansion



Source: World Health Organisation[4]

1 EuroCham's Healthcare Forum is a coordination platform for Sector Committees operating in the Healthcare industry - at present International Quality Generics (The IQMED Generic and Biosimilar), Medical Devices and Diagnostics (MDD SC) and Pharmaceuticals (Pharma Group). The Healthcare Forum enables industry representatives to discuss, share and advocate on common interests and topics. Given its inherently diverse nature, it also covers different interests of those industry representatives. All Sector Committees are equally supported by EuroCham.

2 Clause 3, Article 3 of Circular 15/2019/TT-BYT dated 11 July 2019 of the Ministry of Health: "ICH (International Conference on Harmonization) stands for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use".

3 Report 1085/BC-BYT dated 23 September 2019 of the Ministry of Health.

4 "Health financing for universal coverage", *World Health Organisation*. Available at: <https://www.who.int/health_financing/strategy/dimensions/en/>, last accessed on 28 January 2019.

Patients in Vietnam are currently overburdened with high out-of-pocket payments due to a shortage of quality healthcare facilities outside major urban centres as well as a perception that higher-tier hospital offers better care with patients moving to the city to seek treatment. Therefore, affordable care options are required to reduce the high co-pay burden on Vietnamese patients. While the local drug manufacturing sector has increased availability of local products as per the expansion of Circular 03/2019/TT-BYT[5], a large part of the drug supply relies on import.

The Ministry of Health (MOH) is considering alternative treatment options for the largest number of Vietnamese patients, whilst containing cost of high quality generics, bringing significant savings.

The affordability of treatment is managed at multiple levels: First, at a product/drug level through the Government selection and assessment process; and second, at a service level through patient out-of-pocket costs during a hospital visit.

Affordability is not limited to price. It requires a proper assessment of the real cost of delivering the service in its entirety. The cost of using low-quality therapeutic solutions and the consequences of a medical error or infection has to be taken into consideration. Frequent hospital visits by patients not only increases the pressure on hospital resources, but also exposes the patient to additional service fees, especially for those who have a chronic disease.

Potential gains/concerns for Vietnam

Vietnam is considered to have a high share of out-of-pocket payments, which means that a high proportion of households face severe difficulties managing their income and, subsequently, their health.

Opportunities exist to develop a process that assesses the merits of drugs or products using criteria over and above pricing. This will result in the establishment of a sustainable model of care, based on affordability. The new generic tender Circular[6] does provide a good balance between quality assessment, local manufacturing and price. However, there are still gaps within the process that, if addressed, can further reduce cost and ensure patient safety. Below are some of the issues related to the current process:

- Between each tender group, volume allocation distribution is not clear and varies greatly from hospital to hospital.
- Tender win and quota commitments do not always meet the 80 per cent consumption rate, leading to overproduction for manufacturers which, in turn, drives increased cost.
- The quality control and post marketing surveillance capability of the manufacturer or importer is not a key factor in the tender process.

Recommendations

In the view of our Sector Committee, the Government should review product categorisation, such as branded or generics, in light of experience and data collected in recent years. The process should be revised to ensure that it is delivering the desired objectives, whilst ensuring continuous improvement in cost containment. The introduction of a pharmaco-economy-based assessment will ensure that the cost/effect relationship of products and drugs has been taken into consideration and this, in turn, is more likely to deliver a better distribution of funds.

We also believe that MOH should further facilitate the home treatment concept (out-patients) through favourable reimbursement schemes in order to reduce the number of hospital visits, especially by patients with chronic diseases. This will limit out-of-pocket payment for patients. Our Sector Committee also recommends that the Government:

- Continues an advanced categorisation of the procurement process in Vietnam that will present opportunities for improvement, deliver benefits to the Government and control the budget. Both relevant authorities and key stakeholders have now obtained adequate experience of and insight into the current process of procurement, including the categorisation of drugs. The IQMED - Generic and Biosimilar member companies recommend further detailed discussions about the identified gaps in the process and opportunities for improvement, and;
- The relevant authorities should have measurements for the actual volume which suppliers must strictly commit to deliver.

5 Circular 03/2019/TT-BYT dated 28 March 2019 of Ministry of Health promulgating the list of domestically produced drugs meeting treatment, pricing, and supply requirements.

6 Circular 15/2019/TT-BYT dated 11 July 2019 of Ministry of Health providing guidance on bidding for supply of drugs for public health facilities.

PART 2: BIOSIMILIAR

OVERVIEW

Biological medicines, also known as first-generation biopharmaceuticals, have been produced for the last 30 years and are in clinical use for a number of diseases. Recently, the expiry of many of these product patents has led to the development of other similar biologics at lower costs, with the same safety, purity and potency as their original (reference) medicines. These similar biologics are generally referred to as biosimilars.

Biosimilar medicines are not the same as generic medicines (a medicine which contains exactly the same molecule as an existing chemical medicine, such as aspirin). This is because, unlike chemical medicines, biological medicines cannot be exactly copied. Biosimilar medicines also have nothing to do with complementary, natural or herbal medicines. However, biological medicines (including biosimilar medicines) come from living organisms, such as living cells, that have been modified using biotechnology. This allows these living organisms or cells to produce the active substance of the biological medicine. This active substance is then harvested from the cells. These active substances (e.g. proteins) are usually larger and more complex than those of chemical medicines.

Regulatory pathways for biosimilars

Biosimilars are essential pharmaceutical products that could make important biological medicines available to different markets at an affordable cost. The expiry of patent protection of many biological medicines has led to the need for specific guidance regarding the development and approval of biosimilars. Generally, the term biosimilar refers to a product which is biologically and functionally similar to the reference product, also called originator. By this definition, these medicines can be seen as comparable - but not identical - to the reference medicine. These medicines cannot be deemed as a generic version of their originators, as they are not chemically derived single (small) molecular pharmaceutical entities, which are identical to the original medicines both in pharmaceutical equivalence (identical active substances) and bioequivalence (comparable pharmacokinetics). Moreover, in the case of generics, once the criteria of equivalence are established, these medicines can be waived from clinical efficacy and safety studies. For a biosimilar, the active substance is a protein, which is unlikely to be identical to its reference medicine, precisely because of their biological production mechanisms.

Since the standard generic approach is not applicable to demonstrate similarity of biological/biotechnological derived medicines, the need for specific regulations arises for the registration, production and comparability of these medicines. It seems that the entire world is working towards a framework for developing and approving biosimilars, as demand grows for access to biological medicines at lower prices. That is why many countries are approaching towards the framework of biosimilar regulations.

The European Medicines Agency (EMA) was the first regulatory authority to establish a framework for biosimilar approval, issuing guidelines in 2005. Since that time, the agency has published additional overarching and product-specific biosimilar guidelines and has approved >30 biosimilar medicines. In the past decade, biosimilar guidelines were issued in other stringently regulated markets, such as Australia, Canada, Japan, the Republic of Korea, and the U.S. Furthermore, in 2009, the WHO published guidance aimed at providing "globally acceptable principles" for the evaluation of biosimilars. Intended to assist national regulatory authorities in other regions in licensing proposed biosimilars, the WHO guidelines are regarded as a step toward global harmonisation of biosimilar approval requirements.

Global Harmonisation

According to the regulatory requirements of different regions described in the previous section, there seems to be no significant difference in the general concept and basic principles in these guidelines. There are five well recognised principles with regard to the assessment of biosimilar products: (1) the generic approach is not appropriate for biosimilars; (2) biosimilar products should be similar to the reference in terms of quality, safety, and efficacy; (3) a step-wise comparability approach is required that indicates the similarity of the biosimilar product to reference product in terms of quality is a prerequisite for the reduction of non-clinical and clinical data submitted; (4) the assessment of a biosimilar is based on a case-by-case approach for different classes of products; and (5) the importance of pharmacovigilance is stressed. Establishing biosimilarity allows the biosimilar manufacturer to rely

on the extensive safety and efficacy profile of the originator, hence enabling licensing based on an abbreviated non-clinical and clinical data package. A determination of biosimilarity is based on the totality of the evidence from all stages of the comparison exercise. The step-wise demonstration of biosimilarity includes (1) in vitro analytical testing, (2) nonclinical comparative pharmacology, (3) toxicology, (4) PK testing, and (5) one or more clinical trials to confirm quality, efficacy, and safety of the proposed biosimilar as compared with the reference product.

The European Experience with Biosimilars

The EMA is a decentralised agency of the EU responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. The EU was the first region to develop a biosimilar approval pathway due to the earlier expiration of patents for biotechnology produced medications in European countries.

The EU established legislation for biosimilars in 2004, and EU regulators developed a regulatory approval pathway for biosimilars starting in 2005; the first biosimilar was approved in Europe in 2006.

EMA Guidance

The EMA has provided three guidelines that cover the basic principles, quality, and non-clinical and clinical considerations related to biosimilars:

- The Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues (EMEA/CHMP/BWP/247713/2012): Developed in 2006 and effective since December 2014, this document addresses the requirements regarding manufacturing processes, the comparability exercise for quality, the choice of reference product, analytical methods, physicochemical characterisation, biological activity, purity, and specifications of the similar biological medicinal product.
- The Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1): Developed in 2005 and effective since April 2015, this document describes and addresses the application of the biosimilar approach, the choice of reference product, and the principles of establishing biosimilarity.
- The Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev 1): Developed in 2006 and effective since July 2015, this document provides an overview of the requirements for non-clinical studies and clinical studies when evaluating biosimilar products as well as the risk management plan with special emphasis on immunogenicity.

In addition, EMA has developed individual product-specific guidelines on developing biosimilars. Class-specific guidelines are available for certain types of biosimilar products.

Non-identicality Versus Clinically Meaningful Differences

The EMA's experience with evaluating biosimilars has demonstrated the value of clinical data in the assessment of biosimilarity. The EMA approval standards have been applied to a significant set of candidate biosimilar products and have successfully screened those with substantial analytical and clinical similarity from products with incomplete or unacceptable results.

A majority of biosimilar products reviewed by the EMA have received marketing authorisation. Some biosimilar products that were evaluated by the EMA for marketing authorisation were rejected or withdrawn by their sponsors after the EMA raised concerns during the review process. In one example, the EMA rejected approval of an alpha-interferon biosimilar based on results that showed statistically significant biophysical differences and clinical variations (PK, efficacy, and tolerability) between the biosimilar and reference product treatment groups. Other concerns raised by the CHMP included: impurities, insufficient stability data, significant difference in adverse event rates, and lack of sufficient validation in the immunologic response tests and manufacturing process. Similarly, three applications for human insulin biosimilar candidates in the EU were withdrawn after the products failed to demonstrate PD similarity to the reference product. Finally, a biosimilar of a recombinant human GH is an example of a biosimilar product that received marketing approval by the EMA after initial safety concerns were addressed. In a pre-authorisation clinical study that compared the biosimilar to the reference product, a higher number of patients that received the biosimilar developed non-neutralising anti-GH antibodies as compared to those that received the reference product. Consequently, changes to the purification steps of the biosimilar

product's manufacturing process were made, and the immunogenicity issues were resolved.

There is no expectation for biosimilars to be identical to the reference biologic. The use of unique cell lines and different manufacturing processes results in proteins that have unique structural characteristics compared to the original protein. For example, there have been documented differences in biosimilars in the EU compared to the reference product in terms of PTMs such as glycosylation, phosphorylation, acetylation, and sialylation. These biophysical variations between biosimilar and reference formulations were observed in the absence of statistically significant variations in clinical parameters. In 2013, the EMA approved the first biosimilar antitumor necrosis factor (TNF) mAb. Although some differences in biological activity were detected in an in-vitro assay, this difference was not interpreted to be clinically meaningful since it did not affect the activities of the biosimilar in experimental models regarded as more relevant to the pathophysiological conditions in patients. Regulatory agencies around the world continue to emphasise the importance of clinical testing to evaluate the clinical impact, if any, of these minor biophysical variations.

Why do we need an abbreviated approval pathway for biological products? Experience sharing:

Biological products are the fastest-growing class of therapeutic products in the United States and account for a substantial and increasing portion of health care costs. Congress, through the Biologics Price Competition and Innovation Act, created an abbreviated approval pathway to provide the public with greater access to safe and effective biological products. This pathway provides more treatment options, potentially lowering health care costs through competition and increasing access to lifesaving medications.

The abbreviated licensure pathway does not mean that a lower approval standard is applied to biosimilar or interchangeable products. In fact, as described above, the data package required for approval of a biosimilar or interchangeable product is extensive. If a biosimilar manufacturer can demonstrate that its product is biosimilar to the reference product, then it is scientifically justified to rely on certain existing scientific knowledge about the safety and effectiveness of the reference product to support approval. This allows for a potentially shorter and less costly drug development program for a biosimilar.

Potential safety considerations

An important focus of the development of biosimilars is safety. Developing a biosimilar with a safety profile similar to the reference product can be challenging due to the complex molecular structure and complicated manufacturing process involved. In addition, the molecular structure of biologic products also is sensitive to changes in formulation, packaging, and storage. Safety considerations include immunogenicity, hypersensitivity reactions, and an increased risk for other adverse effects.

Key considerations on potential immunogenicity of biological medicines: Although immunogenicity could be a potential concern for all biological medicines, there are several important considerations: Immunogenicity is not a safety concern in itself. Severe reactions due to an increased immune response are very rare and most often an immune response against a biological medicine is not associated with clinical consequences (e.g. anti-drug antibodies could be transient). The nature of immune reactions depends on many factors: Immunogenicity may be influenced by product characteristics (e.g. changes to the structure of the protein may occur during improper storage or transport, or proteins could form aggregates), but also by treatment-related factors (e.g. the risk may vary with subcutaneous versus intravenous administration or with continuous versus intermittent treatment regimen) and patient- or disease-related factors (e.g. age, genetic and immune status or concomitant treatments). Harmful immunogenicity is unlikely after manufacturing changes or after switching: Many biological medicines are intended for long-term management of chronic conditions, and therefore, over time the patient may receive biological medicines with slight differences. Experience shows that a harmful immune response is unlikely after a change to the manufacturing process of a biological medicine, since comparability studies prove that the batch from the new process is of the same quality and free of impurities or aggregates that can trigger immunogenicity. There is also no reason to believe that harmful immunogenicity should be expected after switching between highly similar biological medicines. Immunogenicity is always monitored post-marketing: Immunogenicity of biological medicines is always monitored by regulatory authorities once the medicine is on the market. This is particularly important to learn of rare immune reactions that can only be detected after a long follow-up period in larger numbers of patients. Immunogenicity data needed for approval of a biosimilar: Clinical immunogenicity studies are generally required for biological medicines. In the case of monoclonal antibodies they are always required, as it is more difficult to predict the incidence of unwanted immunogenicity, the characteristics of the

immune response or the clinical consequences. Such studies look both at short-term immune responses (e.g. infusion-related reactions), as well as long-term (e.g. delayed responses due to an evolving immune reaction).

Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines.

Biosimilars must be distinguished from 'biocopies'

The European Medicines Agency (EMA) defines biosimilars as: "biological medicinal products that contain a version of the active substance of an already authorized, original biological medicinal product (reference medicinal product). A biosimilar agent is similar to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise". The US FDA defines biosimilars as "biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and there is no clinically meaningful difference from the reference product in terms of the safety, purity, and potency." In this context, the distinction between biosimilars and 'biocopies' (alternative terms are 'biomimics', 'intended copies' or 'nonregulated biologics') - versions of monoclonal antibodies or fusion proteins available in countries where regulation is less strict - is of great importance. One of the most significant safety concerns with biosimilars is the potential risk of immune-based adverse events. Because of their molecular size, biologics can directly induce anti-drug antibodies which may have significant consequences for safety. Anti-drug antibodies can also reduce drug levels and affect clinical efficacy, but although available data suggests that biosimilars and their reference products have comparable immunogenicity, this important property might differ between individual biopharmaceuticals.

Biocopies: a biopharmaceutical, claimed to have high similarity with a given reference product, that has not undergone full clinical development and has not achieved regulatory approval according to the regulatory pathway for biosimilars. These biocopies have not been subjected to the same strict analytical, non-clinical and clinical comparative evaluations prior to market approval as biosimilar regulatory pathways mandate. As a result, these products may have clinically significant differences in quality, efficacy and safety from their reference products. Certain biocopies have been shown to have reduced biological potency or higher rates of adverse events, underscoring the importance of following a stringent regulatory pathway for the approval of all biologic medicines. Biocopies are creating confusion among prescribers, and current guidance regarding regulatory pathway, interchangeability and substitution is lacking.

BIOSIMILAR: INCREASING PATIENT ACCESS TO STATE-OF-THE-ART THERAPIES

Relevant Government authorities: Ministry of Health (MOH), Vietnam Social Security (VSS), National Assembly (NA) – Committee on Social Affairs.

Issue description

The development of biosimilars is an attempt to improve access challenges faced by patients, generate cost savings for healthcare systems and increase treatment options for healthcare professionals.

Potential gains/concerns for Vietnam

Benefit for patients:

The introduction of affordable, high-quality biosimilars improves access to life-changing medicines for patients worldwide. The EU saw a 100 per cent increase in the use of biologic treatments after the introduction of biosimilars in the EU.[7]

7 "Biosimilars", *US FDA*. Available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/> last accessed on 28 January 2019. "Delivering on the Potential of Biosimilar Medicines", *IMS Institute for Healthcare Informatics* (2016). Lin-Chau Chang, journal of food and drug analysis 27 (2019) 671-678. Isaacs J, et al. Considerations Med 2017;1:3–6. Anita Krishnan et al. Biosimilars 2015:5 19–32. Kumar et al., J Pharmacovigilance 2015, S3. Richard Markus et al. BioDrugs (2017) 31:175–187. Jun Wang et al. Pharmaceuticals 2012, 5, 353-368.

Benefit for HCPs:

The introduction of biosimilars drives competition, resulting in increased treatment options and value-added services to support patient care and the healthcare community. Between 2016 and 2020, 225 new active substances are set to come to market worldwide, with 30 per cent expected to be biologics.

Benefit to Payors:

Biosimilars introduce competition, increasing the affordability of biologics which delivers savings for healthcare systems, helping to liberate resources that can be used to improve care and fund next-generation medicines. Cumulative savings over the next five years (2016-2021) in the EU5* and the U.S. combined could range from 49 billion EUR to 98 billion EUR.

Health economic benefits from biosimilar medicines (in the EU):

Aging is accelerating in the EU. In supporting the growing elderly population, EU countries will be obliged to spend an increasing proportion of their GDP to provide the required level of healthcare coverage. New and innovative therapies offering irrefutable advances will continue to escalate costs and increase patient expectations. Healthcare expenditure is high on the agenda of every Member State in the EU, with all governments being tasked to deliver the best and most-up-to-date patient care, while at the same time trying to limit the potentially huge increases in associated costs. Over the past 10 years, the introduction of high-quality biosimilar medicines has had a significant impact in reducing healthcare expenditure across the EU. This reduction has helped to manage budgets and allowed better access to important medicines for a greater number of patients.

Recommendations

Based on EU, US experience, the IQMED - Generic and Biosimilar Sector Committee recommends that the Government consider the early issue of regulatory pathways for biosimilar medicines and facilitates the introduction of high-quality true biosimilar medicines to reduce the health expenditure and balance the healthcare expectations.

Biocopies that have not achieved regulatory approval according to the regulatory pathway for biosimilars should be reassessed after the local regulatory pathways for biosimilar medicines have been issued.

The IQMED - Generic and Biosimilar Sector Committee is strongly committed to supporting the Government and relevant State authorities in providing the guidance and regulations on management related to the biosimilars of EMA, US FDA, WHO and members of ASEAN. The IQMED - Generic and Biosimilar Sector Committee is also willing to support in training on verification of application registrating for biosimilar for the experts at Drug Administration of Vietnam, Ministry of Health and the experts verifying applications registrating for biosimilar in Vietnam.

PART 3: TECHNOLOGY TRANSFER, TOLL MANUFACTURING AND LOCAL MANUFACTURING

OVERVIEW

Issue description

Based on the EudraGMDP database, the community database on manufacturing, import and wholesale-distribution authorisations, and Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) certificates maintained and operated by the European Medicines Agency, by the 15th of October 2019, there were 7 companies in Vietnam with 14 granted EU-GMP certificates.[8]

8 The EudraGMP Database, *GMP Compliance*, available at: <http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do>, last accessed on 7 January 2020.

The certificates have been obtained between 2015 and 2019, which equates to 3.2 EU-GMP certificates per year. This represents only a marginal fraction compared to the number of EU-GMP granted during the same time in Germany (1646), Poland (1140), France (934), the United Kingdom (917), United States (380) or Hungary (277).[9]

Table 2: EU-GMP certificates granted to the pharmaceutical companies located in Vietnam

Certificate Number	Eudra GMDP Document Reference Number	Document Type	Site Name	Address	City	Country	Inspection End Date
OGYÉI/22758-6/2019	64139	GMPC	SaVi Pharmaceutical Joint-stock Company	Lot Z01-02-03a Industry Zone, Tan Thuan Export Processing Zone, Tan Thuan Dong Ward, District 7.	Ho Chi Minh City	Vietnam	2019-08-30
DE_HE_01_GMP_2019_0194	56788	GMPC	STELLAPHARM J.V. CO., LTD. - BRANCH 1	No. 40 Tu Do Avenue, Vietnam - Singapore Industrial Park, An Phu Ward, Thuan An Town	Duong Province	Vietnam	2019-03-07
482760-0001	53446	GMPC	BTH Ho Chi Minh City Blood Transfusion Hematology Hospital, Bloodbank	118 Hong Bang Street, District 5	Ho Chi Minh City,	Vietnam	2018-12-06
FT072/S1/MH/001/2018	51726	GMPC	Branch of ImexPharm Corporation	Vinh Loc Hi-Tech Pharmaceutical Antibiotic Plant, Lot B15/I - B16/I, Street 2A, Vinh Loc Industrial Park, Binh Hung Hoa B Ward, Binh Tan District	Ho Chi Minh City	Vietnam	2018-09-21
DE_HE_01_GMP_2018_0127	50764	GMPC	Pymepharco Joint Stock Company	166-170, Nguyen Hue Street, Tuy Hoa City, Betalactam Sterile Manufacturing (Block B)	Vietnam	Vietnam	2018-01-31
MED09/2018/001	48020	GMPC	MEDOCHEMIE (FAR EAST) LTD., (LIQUIDS AND SEMI-SOLIDS FACILITY)	No. 10, 12 and 16 VSIP II-A, Street 27, Vietnam-Singapore Industrial Park II-A, Vinh Tan commune	Tan Uyen town	Vietnam	2017-12-14
MED08/2018/001	48037	GMPC	MEDOCHEMIE (FAR EAST) LTD., (ORAL FACILITY)	No. 40, VSIP II Street 6, Vietnam-Singapore Industrial Park II, Binh Duong Industry-Service-Urban Complex	Thu Dau Mot city	Vietnam	2017-12-14
DE_HE_01_GMP_2017_1064	45079	GMPC	Pymepharco Joint Stock Company	166-170, Nguyen Hue Street, Tuy Hoa City,	Vietnam	Vietnam	2017-10-03
BG/GMP/2017/098	42251	GMPC	Tenamyd Pharmaceutical Corporation	Lot. Y.01-02A Tan Thuan Industrial Park/ Export Processing Zone, Tan Thuan Street Tan Thuan Dong Ward, District 7	Ho Chi Minh City	Vietnam	2017-04-07

9 The EudraGMP Database data for period from 1 October 2015 until 21 December, 2019, *GMP Compliance*, available at: <http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do>, last accessed on 7 January 2020,

MED10/2017/001	48057	GMPC	MEDOCHEMIE (FAR EAST) LTD., (ASEPTIC CEPHALOSPORIN FACILITY)	No. 10, 12 and 16, VSIP II-A, Street 27, Vietnam-Singapore Industrial Park II-A, Vinh Tan commune	Tan Uyen town	Vietnam	2017-03-15
UK GMP 46387 Insp GMP 46387/14673770- 0001	39282	GMPC	PHIL INTER PHARMA COMPANY LIMITED	NO. 20, HUU NGHI BOULEVARD, VSIP	THUAN AN, BINH DUONG	Vietnam	2016-10-11
UK GMP 46387 Insp GMP 46387/15275896- 0001	39281	GMPC	PHIL INTER PHARMA COMPANY LIMITED	NO. 25, STREET NO. 8, VSIP	THUAN AN, BINH DUONG	Vietnam	2016-10-11
ES/141HV/16	38540	GMPC	IMEXPHARM CORPORATION BRANCH	Vietnam Singapore industrial Zone II, Thu Dau Mot City	Thu Dau Mot City	Vietnam	2016-02-15
SK/033V/2015	33294	GMPC	Tenamyd Pharmaceutical Corporation	Lot. Y.01-02A Tan Thuan Industrial Park/ Export Processing Zone, Tan Thuan Street Tan Thuan Dong Ward, District 7	Ho Chi Minh City	Vietnam	2015-10-29

Source: The EudraGMP Database

This shows there is no footprint yet and Vietnam is only at the very beginning of the tech transfer era.

With the urge for increased foreign pharmaceutical companies' investments and technology and know-how transfers communicated by the local government, one could expect an existing facilitation system for the investors.

As of 1 July 2018, the new Law on Technology Transfer 2017[10] took effect, replacing the Law promulgated in 2006. It has embodied several progressive provisions that would further encourage technology transfer activities in Vietnam. However, the companies planning technology transfer will still encounter many obstacles.

While considering Vietnam as a place for tech transfer, investors' concerns will include three groups of variables:

1. Infrastructural

- Lack of suitable facilities;
- Lack of experience in high-quality medications manufacturing, including lack of domestic suppliers of pharmaceutical high technologies (machinery, software), QC and calibration services, long waiting time for the lab results;
- Limited number of highly-qualified employees and a lack of professional training to improve the knowledge and skills of employees; and
- Vietnam grants an abundance of tax exemptions and incentives especially for high technologies but it is essential to check the details and durability of these (compare different provinces, locations, for example special industrial zones), otherwise it may lead to high unexpected investment costs (especially related to environmental protection). Vietnam also set a special support fund for high technologies but no foreign investors have access to it.

10 Law 07/2017/QH14 dated 19 June 2017 of the National Assembly on technology transfer.

2. Technical barriers

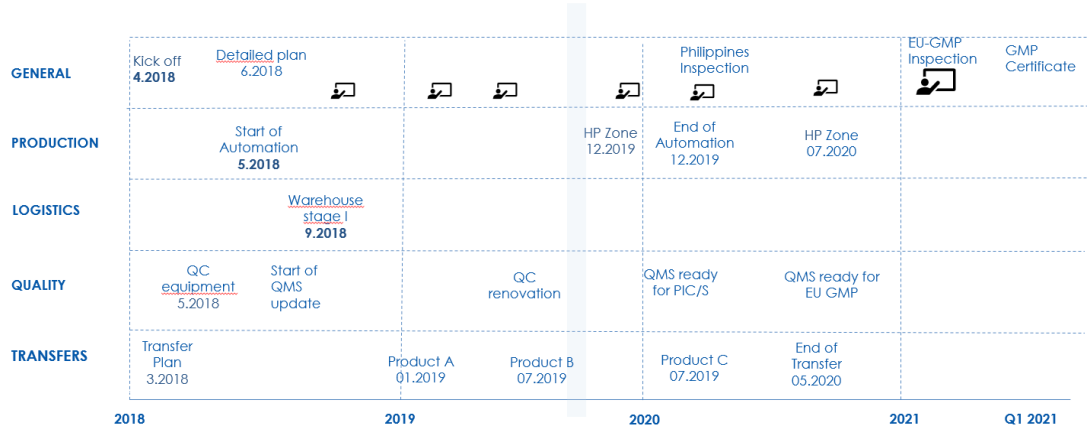
- Although the regulations on trial production are implemented in Vietnam and based on the general guidance of the WHO, in practice, the procedures of API deliveries for validation series (pilot production) before obtaining product license are very difficult;
- With Decision 18/2019/QĐ-TTg [11]dated 19 April 2019 in place, regulating the import of used machinery, equipment and technological lines, the criteria and procedures for importing used machinery are clear. However, they remain challenging for investors, especially when the company wants to move the production lines and machinery from the foreign factory to the local plant of the same producer;
- Lengthy and complicated customs procedures (machines delivery); and
- Weak execution of Intellectual Property protection and non-disclosure, threat of stealing transferred technologies. In 2019, the Law on Intellectual Property was amended, creating a favourable legal environment for both local and foreign organisations and individuals. The reintroduction of the compulsory registration of technology transfer agreements has raised concerns among the involved parties. Related laws state that a technology transfer agreement will become effective only when the agreement is registered with the authorities, while the process of registration is often prolonged (by up to one or two months). Without carefully devised solutions to minimise the IPR risks associated with technology transfer, investors may suffer a loss of competitiveness and market share as a result of losing their IPR to local competitors. It should be clarified that foreign licensors in the medical sector are not obliged to disclose the content of new diagnostic or treatment methods prior to signing a technology transfer contract for approval by the Ministry of Health.

3. Market access factors

- Currently, regulations on production, distribution, and tendering in Vietnam are encouraging and creating advantages for the medicines technology transfer. Therefore, domestic manufactures and FDIs in Vietnam are taking effors to enhance their factories to obtain EU-GMP standards and accept the technology transfer. Medicines with transferred technology that have been produced in the factories which obtained EU-GMP will be classified into the Group 1 or Group 2 in the hospital tenders. However, it still does not guarantee the production utilisation, therefore this is still the reason for investors' hesitation to justify the investment time and value;
- Tech transfer doesn't guarantee export; and
- There is a prolonged and laborious drugs registration process.

11 Decision 18/2019/QD-TTg dated 19 April 2019 of the Prime Minister on import of used machinery equipment and technological lines.

Table 3: EU-GMP implementation timetable based on tech transfer by an international company with local manufacturing operations in Vietnam



Potential gains/concerns for Vietnam

Technology transfer can bring clear benefits to Vietnam's economy. The key gains are as follows:

- Up-scaling of the local pharmaceutical industry (high volume with high quality but also increasing quality standards within other local manufacturers, even those without EU-GMP or equivalent standards);
- Knowledge transfer (know-how, local medicines dossier development);
- Scalability: Even if the new facilities are not available any longer, the existing EU-GMP companies can render toll and contract manufacturing services and produce more local high- quality medicines.

All of the above will increase Vietnam's drug safety (sufficient supply) and ensure Vietnamese patient safety, which should definitely be considered as a major opportunity and by all means translated into the country's gain resulting from the pharmaceutical technology transfer.

Also, technology transfer can help in transforming healthcare to provide universal coverage, the most critical healthcare priority in Vietnam today. The Government aims to reach 90 per cent of the population with access to public healthcare insurance by 2020.[12]

The proper approach to ease technology and know-how transfers will not only achieve early patient access to high-quality medicines but also ensure efficient public spending on healthcare management. Key positives for Vietnam's healthcare industry could be derived from adopting best practice in other markets. These include:

- Sustaining high-quality local medicines for Vietnamese patients with reliable pricing;
- Ensuring efficiency in Government spending; and
- Ensuring the reliability of local manufacturers for Vietnamese patients.

12 Prime Minister Nguyen Xuan Phuc's speech at the National Health Insurance Teleconference on 3 June 2016.

Recommendations

Evaluating current infrastructure and legal conditions, the IQMED Sector Committee proposes that the Government implements 3 major easements which will support the initiative of technology transfer in Vietnam:

- Fast-track for registration of all products manufactured on EU-GMP or equivalent production lines with a clear timeline for specific steps;
- The Government should ensure clear benefits for manufacturers implementing high-quality standards such as EU-GMP and equivalent by setting the guarantee of utilisation respective quotas, for example volume-based long-term contracts and higher scoring methodology in tenders; and
- Improvements and incentives for tech transfer implementation, among others:
  - Short and clear custom procedures;
  - Good Distribution Practise (GDP) standards to secure proper transportation conditions to Vietnam and within the country;
  - List of the approved suppliers of API;
  - Access to nationwide tax incentives and environmental facilities for all companies running tech transfer.

The EuroCham IQMED - Generic and Biosimilar Sector Committee is strongly committed to further collaborating with the Government to bring global expertise, best-practice sharing, models and tools in planning and implementing these activities.

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EuroCham International Quality Medicines – Generic and Biosimilar Sector Committee